REMARKS

Claim 1 has been amended to correct the obvious error kindly noted by the Examiner. Claims 34 and 35 have been amended for clarification to correct the lack of clarity also noted by the Examiner. As the amendments amount only to correction of an obvious error and the clarification requested by the Examiner, it is believed that entry of the amendment though made after final is appropriate, and entry of the amendment is respectfully requested.

Applicants further are grateful for the indication at the interview that the amendment would be entered after final as the substantive issues are not affected by the amendment.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

This basis for rejection is obviated by amendment. Applicants appreciate their attention being called to the need for this rephrasing of the claims.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

This basis for rejection was grounded in the assertion that the requirement that the "liposomes are not polymerized" is new matter. Respectfully, applicants point out that the situation is indeed analogous to that in *Kennecott Corp. v. Kyocera Int'l, Inc.*, in that it is quite clear from the application as written that the liposomes are not polymerized. The reason this is so is that an active polymerization step would be required in order to obtain polymerized liposomes. No such step is ever performed in any of the examples, nor is there any suggestion in the specification itself that this extra step should be taken. As noted in the cited Nagy, *et al.,* document (U.S. 7,285,289) at column 12 at lines 23-26, polymerization involves chemical crosslinking of molecular monomers to one another by exposure to UV light or other polymer-promoting catalysts. No such steps are taken in describing the preparation of liposomes in the present invention. In the exemplified preparations

of Nagy, for example, the liposomes in example 1, polymerization is conducted by UV light irradiation (column 17 line 5). Similarly, in example 2, column 18 lines 1-2, the liposomes are polymerized by exposure to UV light for approximately five minutes. There is no such step conducted in the present application. Standard liposomes are simply not polymerized. The present application describes only standard liposomal preparations.

Therefore, the explicit statement in the claims of the inherent properties of the liposomes described in the specification is not new matter, and the discussion at the interview seemed to indicate that Examiner Chen is now in agreement with this position. Withdrawal of this basis for rejection is therefore respectfully requested.

The Rejection Under 35 U.S.C. § 103

The sole remaining rejection of all claims is based on the combination of Craig, *et al.* (WO97/28818) in view of Gregoriadis, *et al., Methods* (1999) 19:156-162, Nagy, *et al.* (U.S. 7,285,289) and Gregoriadis, *et al.* (U.S. 7,008,791).

Applicants acknowledge that Craig describes administering both a nucleic acid encoding an antigenic protein and a peptide that could be considered the equivalent of the "assistor protein" of the present claims, but does so by disclosing a broad genus of approaches to delivering these active components. As applicants have argued previously, while liposomes are mentioned as delivery vehicles that could be employed in one of the many embodiments and designs for delivery of the nucleic acid and the assistor protein, this is clearly not a preferred embodiment, *nor is there any positive suggestion that both the nucleic acid and the assistor protein be associated with the same liposomes*.

The only two occasions on which liposomes are even mentioned do not even imply that both the nucleic acid and the assistor protein be associated with the same liposomes. The mention of liposomes among a laundry list of delivery vehicles, at page 12 line 23, is at best ambiguous and the other mention, on page 24, envisions liposomes which contain only nucleic acid, and which are targeted. Thus, Craig falls short of disclosing even the requirement that the nucleic acid encoding the antigenic protein and the assistor protein are associated with the same liposomes, much less the specific arrangement of components therein required by the present claims.

Gregoriadis (*Methods*) does not remedy this as the cited article only describes liposomes that are delivery vehicles for DNA and proteins in the alternative. Nagy does not remedy this because Nagy effectively teaches only delivery of proteins. To the extent nucleic acids are included among the antigens described by Nagy, these are not taught to be included in the same liposomes as proteins, or taught to be in the intravesicular space. The only mentions of the use of nucleic acids in Nagy at all are in column 8, at lines 30-32, where nucleic acids are included among a laundry list of possible antigenic materials, and in a similar laundry list in column 11, lines 50-54. In any event, all of the antigens are supposed to be displayed on the carrier. And, indeed, the carrier must be polymerized, unlike the liposomes of the present invention from which polymerized liposomes are excluded. At least according to the claims of Nagy, the liposomes must also be free of phospholipids, which are required by the present claims. On these bases alone, Nagy is at best irrelevant.

Gregoriadis ('791) also does not remedy this deficiency as it discusses only DNA vaccines *per se*, not any suggestion to combine both a nucleic acid encoding an antigen and an assistor protein in the same liposome. The presence of nucleic acid in the intravesicular space when the

nucleic acid is the only active ingredient does not bear on its preferred location in the context of the present invention, and this is only one of two alternatives suggested in this document.

As presented at the interview, Exhibit A summarizes the disclosures of the secondary documents. The secondary documents do not focus on the limitations of the claims, but provide a variety of arrangements. Even if they could be said to suggest, as Craig does not, that the nucleic acid encoding the antigenic protein and the assistor protein be included in the same liposomes, the limitations of the present claims do not follow.

Gregoriadis (Methods) describes entrapping either DNA or protein in liposomes in the intravesicular space (see Table 4 of Gregoriadis for entrapping proteins). Nagy is concerned with exhibiting multiple copies of either proteins or DNA on either the surface or in the interior of liposomes which are not composed of phospholipids and which are polymerized. In column 4, at line 50, Nagy indicates that the antigens may be presented on the exterior or interior of the particle and Figure 7, for example, shows the antigens in the interior. Further, either proteins or DNA could be displayed (see column 8, line 31).

Gregoriadis ('791) discloses either entrapping DNA or complexing DNA with lipids. These are presented in the alternative in claim 1, for example, and in column 3, line 63.

Thus, far from suggesting the specific combination required by the claims – *i.e.*, that the antigenic protein is on the surface and the nucleic acid is entrapped in the intravesicular space of the liposomes, one could equally have chosen:

- from Gregoriadis (Methods) protein entrapped in the intravesicular space, in combination with
- nucleic acids on the surface as disclosed in Nagy or with;
- DNA complexed (and therefore on the outside of) liposomes as taught by the Gregoriadis patent.

It would appear that only by already knowing that the claims require entrapping DNA in the intravesicular space and protein on the surface would it be possible to make the particular selections from the two Gregoriadis documents and from Nagy that the Examiner has made. As applicants are sure the Examiner would agree, using the invention as a guide to make the appropriate selections from various documents is inappropriate. The specific combination needs to be suggested by the documents themselves.

A relevant, illustrative case is *In re Wesslau*, 353 F2d 238, 147 USPQ 391 (CCPA 1965), where the Court stated that it is impermissible to choose only so much of the disclosure of a document as will support the position taken by the Office while ignoring what the reference as a whole suggests. In that case, the claims were directed to an improvement in a polymerization process that required a particular group of catalysts. The PTO was able to find documents that disclosed the various catalysts involved. In one document, Anderson, the disclosure of the catalyst was taken out of context ignoring the implication of the entire teaching that the nature of the catalyst was not important to achieving the improvement in polymerization that was claimed.

Similarly, here, for example, Gregoriadis '791 implies that it does not matter whether DNA is entrapped or complexed to the exterior are liposomes; Nagy discloses that it does not matter whether the multiple biological agents are on the surface or the interior of the polymerized non-phospholipid liposomes, and Gregoriadis (Methods) discloses that either protein or DNA could be entrapped in the intravesicular space. By extracting only so much of the document as is supportive, the Office has ignored the overall teachings of each of the secondary documents. For that matter, the overall disclosure of Craig would imply that it does not matter whether liposomes are used or any other delivery method.

In addition, as discussed at the interview, the only document that even suggests proteins (as well as DNA) might be at the surface (as well as in the interior) is Nagy and Nagy specifically does not deal with the liposomes of the present invention. Nagy requires, by its claims, that phospholipids not be included and that the liposomes be polymerized. Neither of these features are permitted in the liposomes of the present invention. If Nagy is not available, there is no document of record which suggests proteins be displayed on the surface of liposomes.

Applicants also point out that the disclosure of the enormous genus of possibilities that are provided by Craig even in combination with the two Gregoriadis documents and Nagy is insufficient to suggest the specific combination required by the claims. The claims specifically require intravesicular DNA, surface displayed assistor protein and phospholipid containing non-polymerized liposomes. This species of the very broad genus suggested by Craig, even with the addition of the secondary documents does not defeat patentability of the species. A perhaps simpler manifestation of this is the decision in *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In that case, a known herbicide, dicamba, was claimed as a specific salt with a particular ammonium ion. The document disclosing dicamba as an herbicide listed a multiplicity of such salts, one subgenus of which included the specific salt claimed. The ammonium compound that represented the cation of the salt was disclosed in other, secondary documents, although not as an herbicide. The Court found that there was no reason for the applicant to pick out that particular ammonium salt to provide the claimed herbicide, event though that salt was known.

There is much less motivation here to make a specific choice from each of the secondary documents which happens to coincide with the invention without the guidance of the invention to indicate which choice to make. This on top of the failure of any document to suggest surface

display of proteins on the types of liposomes included within the claims. This element is entirely missing.

Conclusion

While Craig suggests co-delivery of antigenic proteins and nucleic acids encoding them in the same vaccine, Craig discusses a very large genus of forms as to the specific nature of these vaccines and methods of delivery. Liposomes are casually mentioned among many possible delivery methods and never specifically exemplified or indicated as desirable, and there is clearly no suggestion that the nucleic acid and the assistor protein be associated with the same liposomes. There is certainly no suggestion that their association take the form required by the claims with the nucleic acid in the intravesicular space and the assistor protein displayed on the surface.

None of the secondary documents remedy these deficiencies. None of these documents even suggest placing both nucleic acid and protein in the same liposomes, their teachings are applied to Craig only because the present invention itself suggests doing so. In any case, each of the secondary documents suggests at least two alternatives, only one of which fits the limitation of the claims. Without the invention as a guide, the selection of the appropriate alternatives from each document would not be possible, as shown in Exhibit A. Further, no document whatsoever suggests the claim limitation that proteins be exhibited on the surface of liposomes of the types included in the claims.

The requirement that the liposomes used in the composition of the invention be non-polymerized is not new matter. As noted, an active step of polymerization, which is not anywhere provided in the application, is required in order to achieve polymerized liposomes. Standard preparation of liposomes simply does not result in polymerized forms. Also, the liposomes of Nagy

exclude phospholipids, which are a mandatory component of the liposomes of the present claims. These are further distinctions from the Nagy document, in particular, which is the only document describing display of antigens on the surface of liposomes.

Thus, the combination of documents as cited fails to teach phospholipid-containing liposomes that are not polymerized with protein in antigenic form on the surface and fail to teach nucleic acids and antigenic proteins contained in the same liposomes in the manner required by the claims.

Accordingly, applicants believe that claims 13, 16, 25-26, 28-30 and 32-35 are in a position for allowance and passage of these claims to issue is respectfully requested.

Again, applicants wish to express their appreciation to Examiner Chen for his thoughtful discussion at the interview with the undersigned.

Should minor matters remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 429022000800.

Respectfully submitted,

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